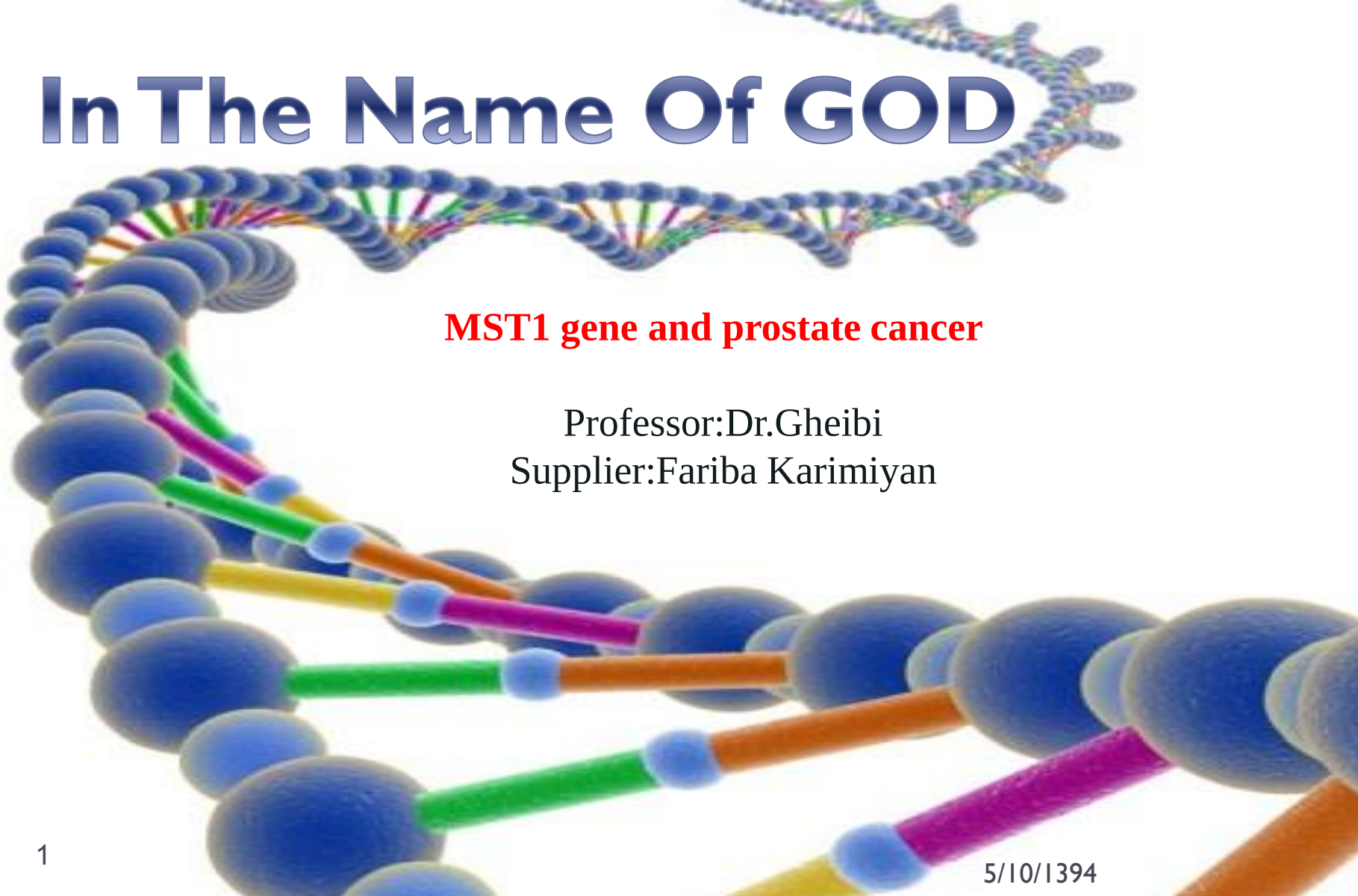
In The Name Of GOD



MST1 gene and prostate cancer

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contents

MST1 gene(1)

- A protein kinase of the STE20 family.

- Alternative names:
  Serin Threonin Kinase 4 ; STK4
  Kinase Responsuve To Stress 2; KRS2

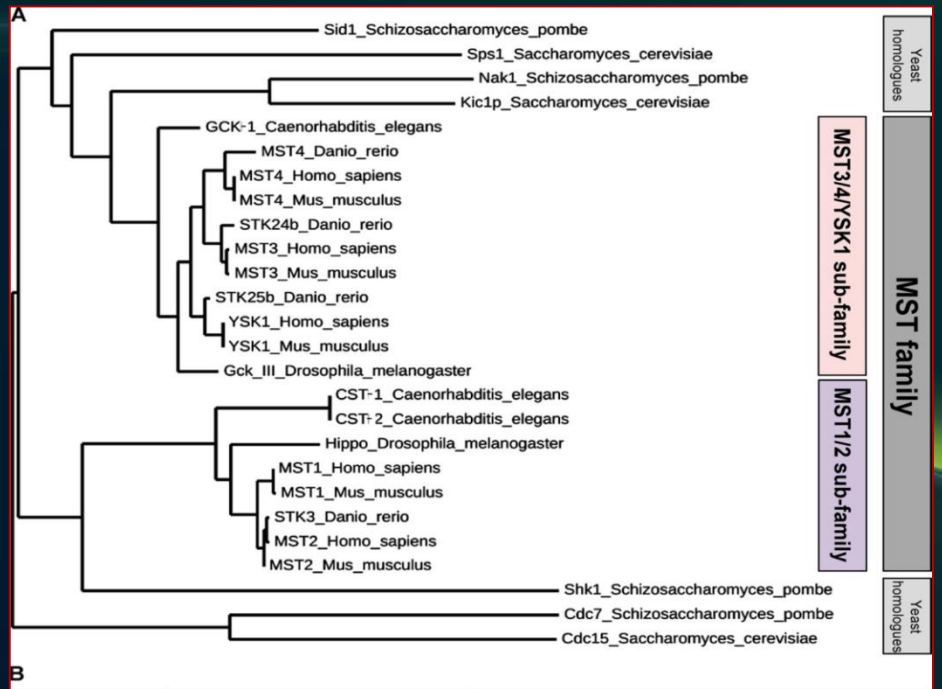
- MST kinases subgroups
  - MST1(STK4), MST2(STK3)
  - MST3(STK24), MST4(STK26),YSK(STK25)

MST1gene(1)

- **Chromosomal Location : 20q11.2-q13.2**

- **Disease: T-cell Immunodeficiency, Recurrent Infections, And Autoimmunity with or without Cardiac Malformations (TIIAC) caused by mutations affecting the gene**

Classification(2)



S. cerevisiae	Cdc15		Kic1/Sps1		
S. pombe	Sid1/Cdc7/Shk1		Nak1(Orb3)/Pkp11		
D. melanogaster	Hippo		GckIII		
C. elegans	Cst1/2		GckI		
D. rerio	STK3		STK24b	MST4	STK25b
Mammals	MST1/STK4	MST2/STK3	MST3/STK24	MST4/MASK	MST5/STK25/YSK1

MST kinase family

MST1 kinases

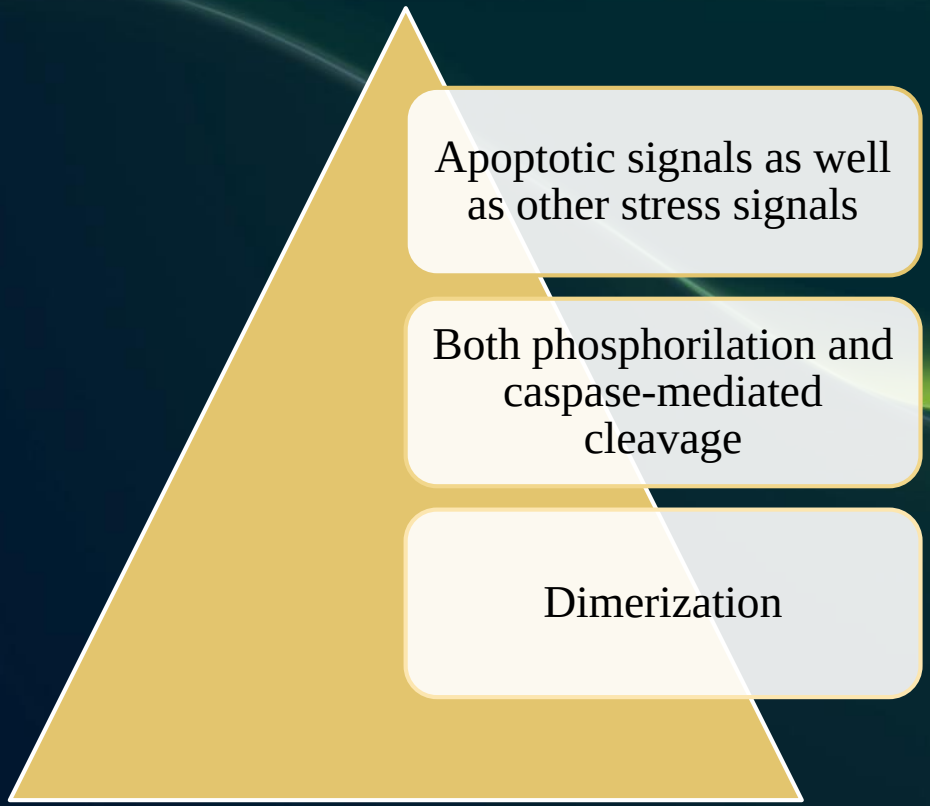
- Emerging as key signaling molecules that influence:

  cell proliferation, organ size, cell migration, and cell polarity

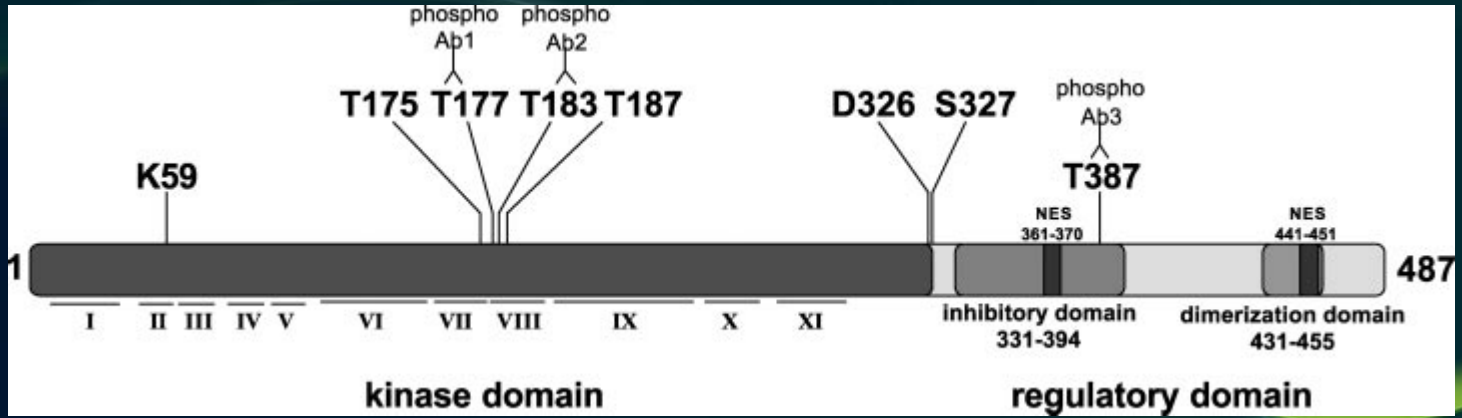
- Studies in this field are focuse on:

regulation and function of these kinases in normal physiology and pathologies, including cancer, endothelial malformations, and autoimmune disease(2)

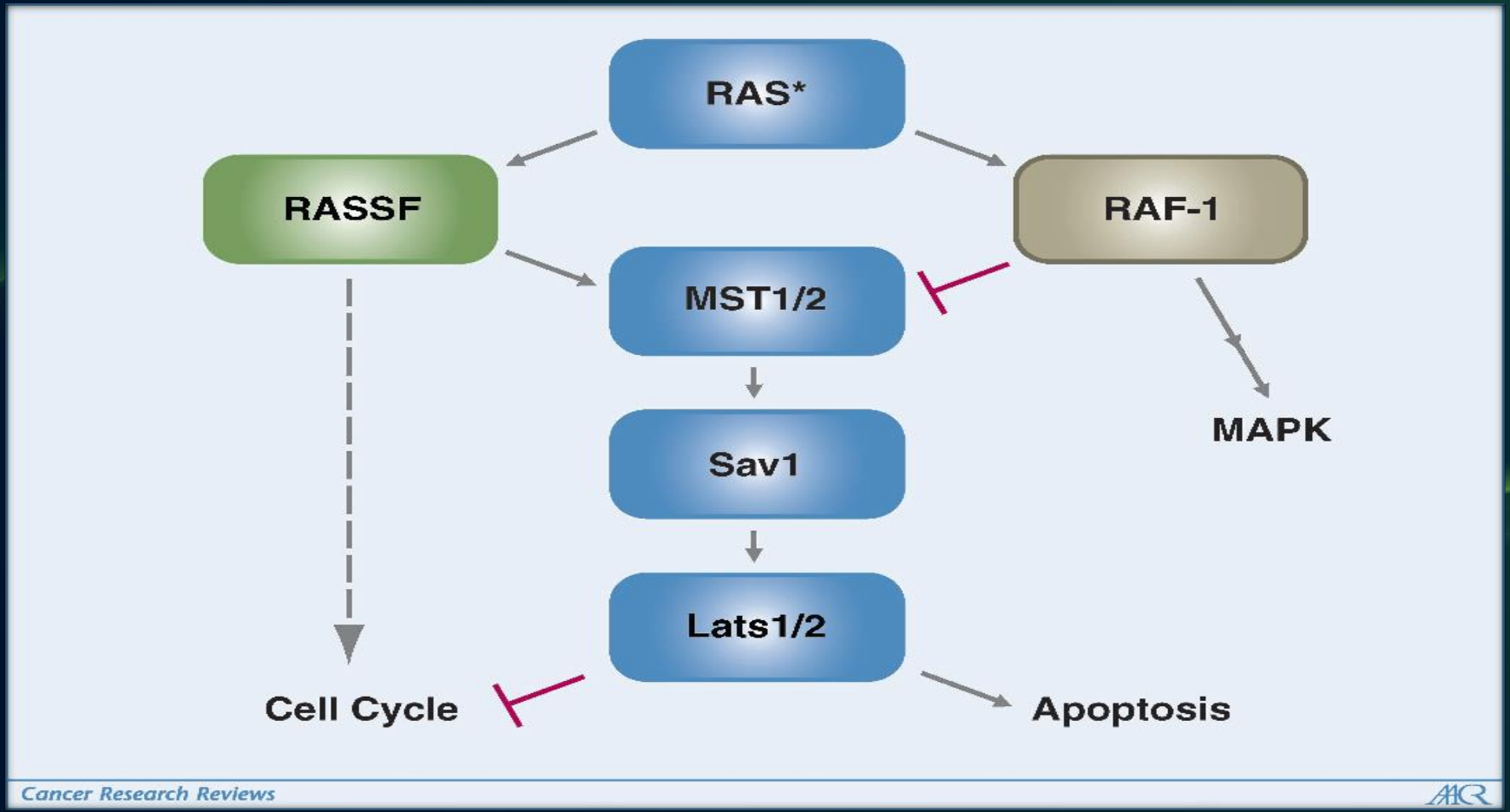
MST1 activation



Schematic representation of MST1 kinase.

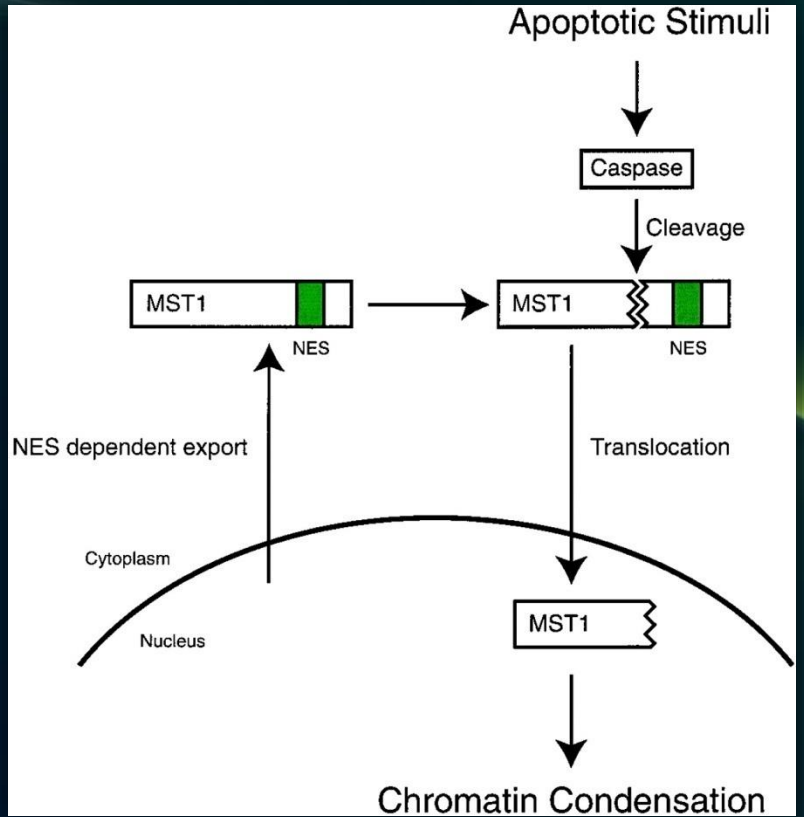


Two residues (Thr183 and Thr187) within the MST1 activation loop are essential for kinase activation(3)

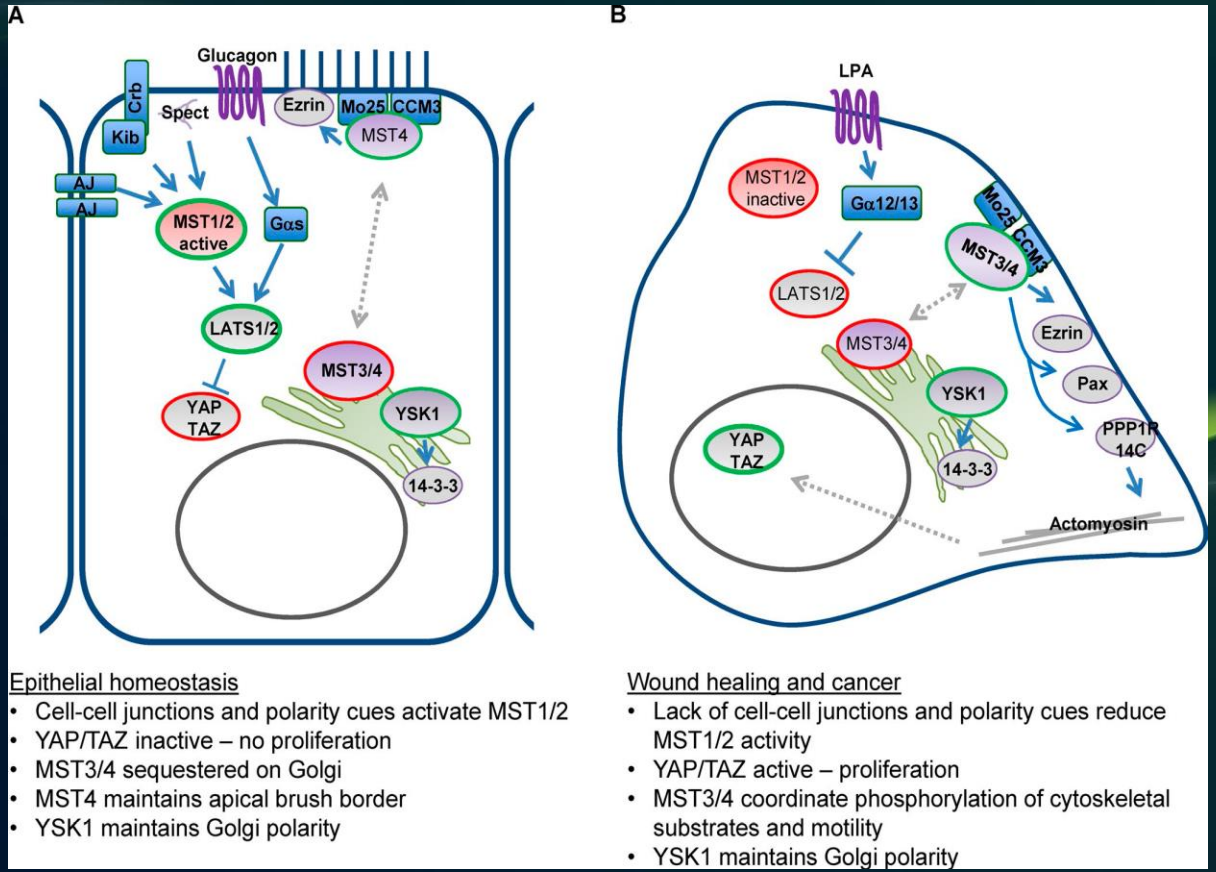


MST1 activation through Raassf and simultaneous removal of negative regulation by Raf-1(2)

The role of MST1 in apoptosis(4)



The role of MST1 in hemoestasis,wound healing and cancer(2)



Epithelial homeostasis

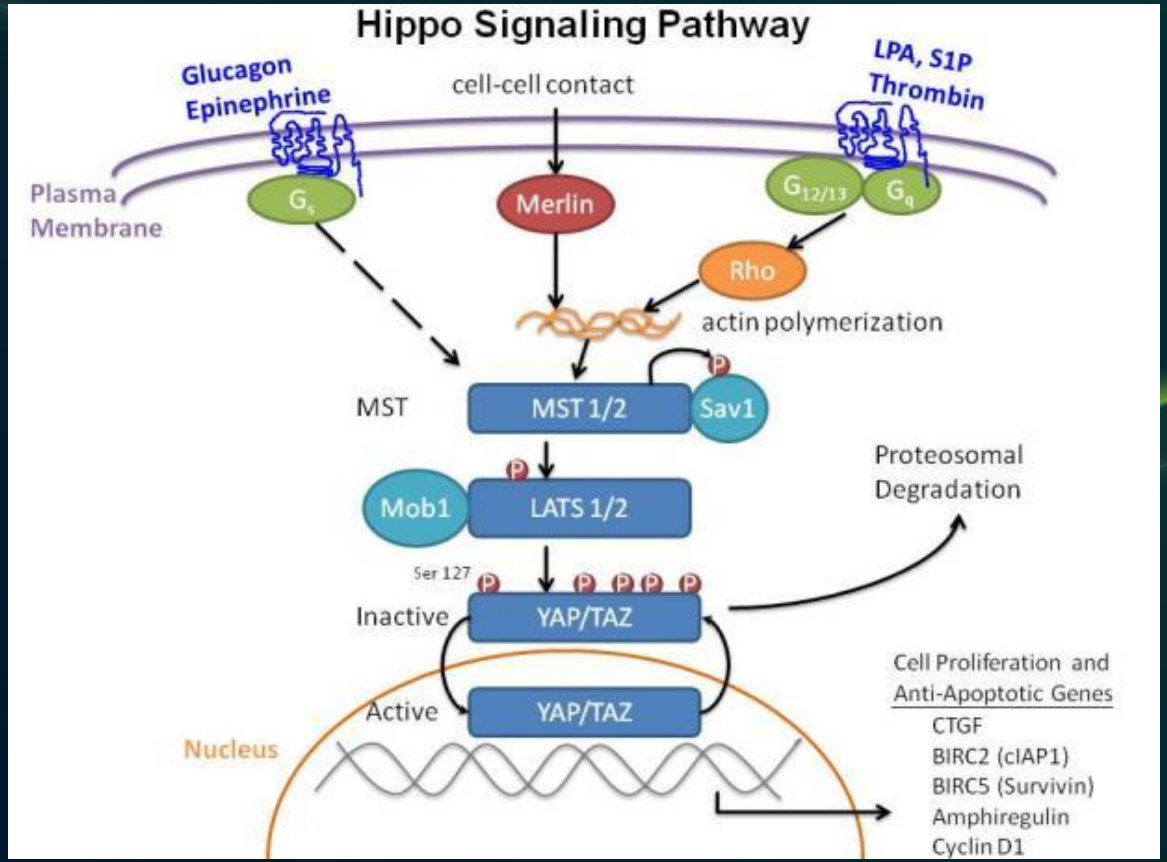
- Cell-cell junctions and polarity cues activate MST1/2
- YAP/TAZ inactive – no proliferation
- MST3/4 sequestered on Golgi
- MST4 maintains apical brush border
- YSK1 maintains Golgi polarity

Wound healing and cancer

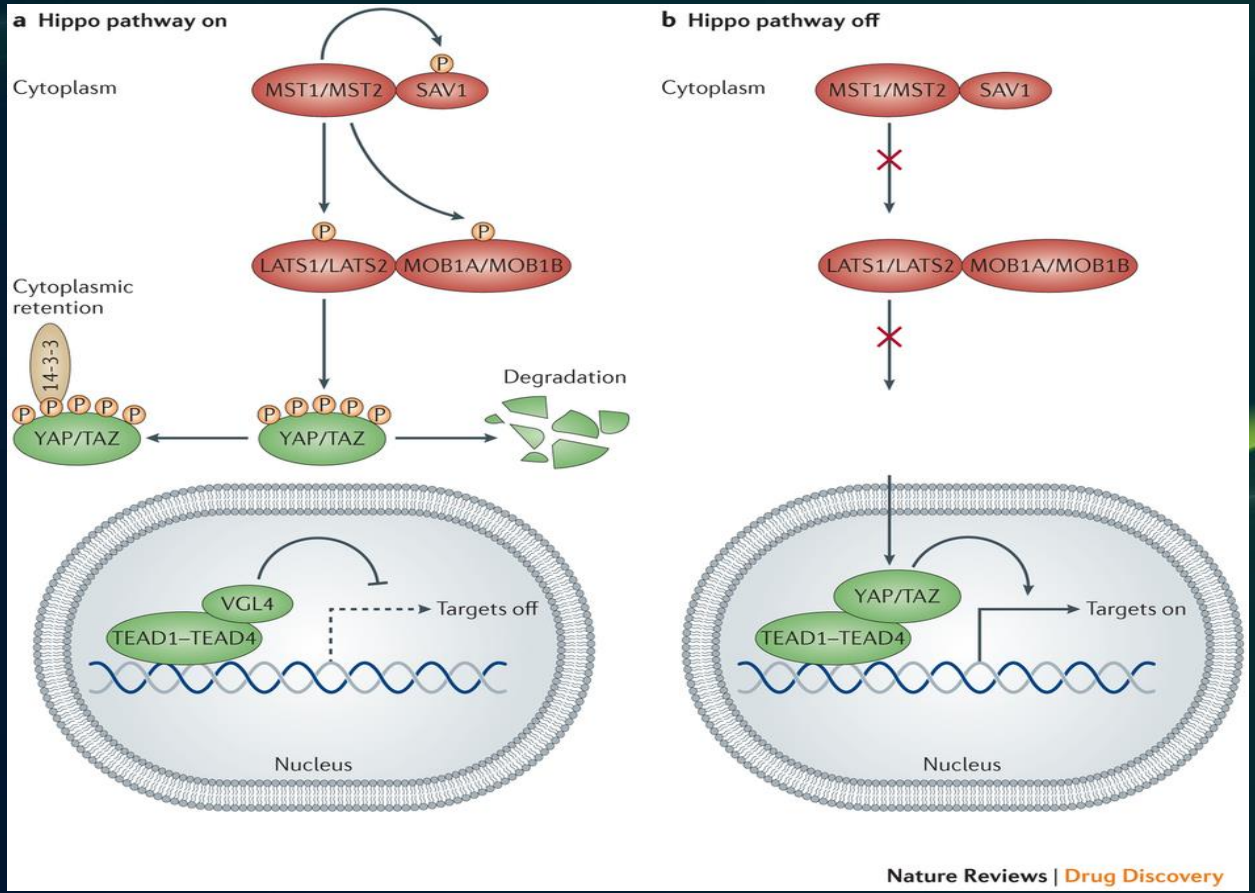
- Lack of cell-cell junctions and polarity cues reduce MST1/2 activity
- YAP/TAZ active – proliferation
- MST3/4 coordinate phosphorylation of cytoskeletal substrates and motility
- YSK1 maintains Golgi polarity

Hippo signaling components(5)

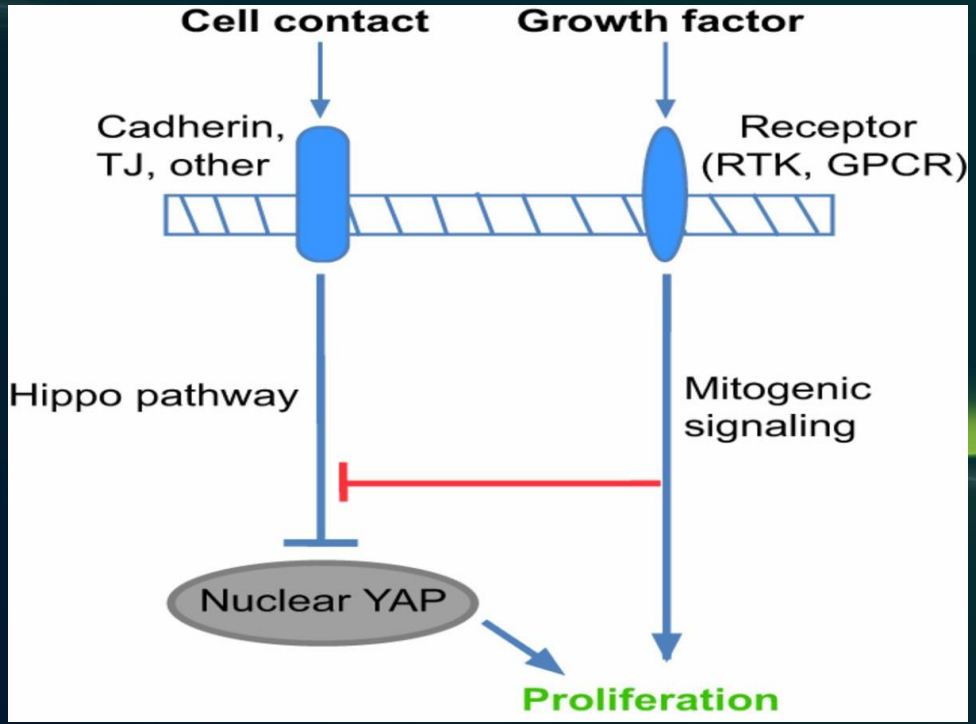
Amphiregulin
BIRC5
cIAP1
CTGF
Cyclin D1
Galpha s
Galpha 12/13
Lats1/2
Mob1
Mst1/2
Rho A
Sav1
TEADs
Yap/Taz



Hippo signaling pathway(6)



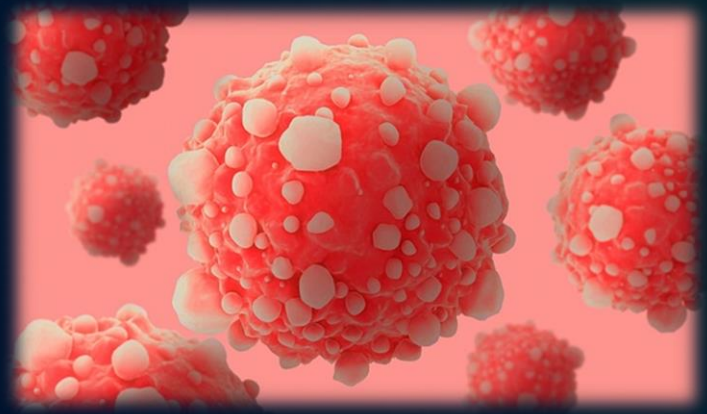
Hippo signaling regulation(7)



The Hippo pathway mediates the reciprocal regulation of cell proliferation by contact inhibition and mitogenic signaling

MST1 and cancer

- In order to importance affects of MST1/Lats signaling pathway on cell proliferation,it seems that these kinases has an important role in cancers pathology



MST1 and cancer

- Hippo-Lats-Yorkie signaling regulates tissue overgrowth and tumorigenesis in*Drosophila*.
- Mst1 and Mst2 protein kinases;the mammalian Hippo orthologs.
- Mst1/2 inhibition of Yap1 is an important pathway for tumor suppression in human HCC.(9)

MST1 and pathologeis

- Loss of MST1 made mouse susceptible to autoimmune diseases including skin lesions around eyes along with enlarged spleen

- The occurance of the SNPs on MST1 are related to Crohn disease and colitis(10)

Prostate Cancer

- Prostate cancer has become a major public health problem in Western industrialized countries.
- Most prostate cancers are very slow growing, but some can grow and spread quickly
- If the cancer is discovered before it spreads beyond the prostate gland it is potentially curable
- Prostate cancer is usually found during a routine physical examination (11)

Signs & symptoms(11)

In the early stages, there may be no symptoms

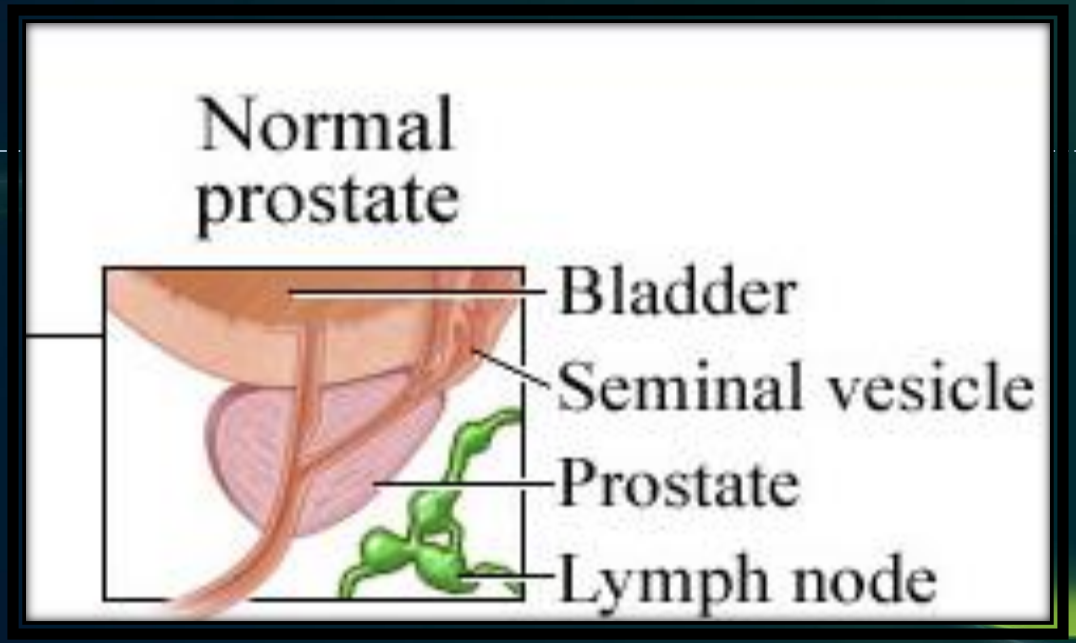
As men age, the prostate can become enlarged for a number of reasons

These symptoms don't mean that cancer is present:

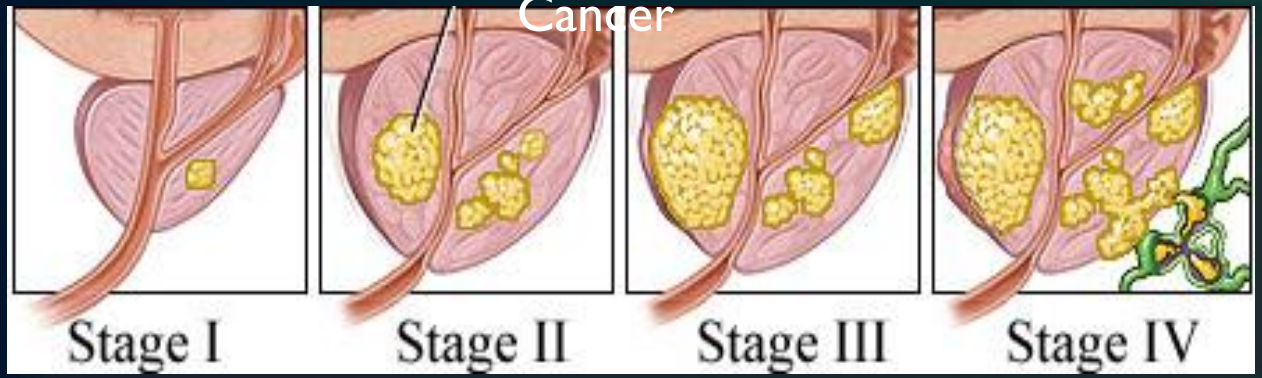
- starting or stopping urination is a problem
- slow stream
- painful urination or ejaculation
- dribbling
- frequent urination
- loss of urinary control
- blood in urine or ejaculate
- night-time voiding

In advanced cases of prostate cancer, symptoms can include:

1. Weight lose
2. Fatigue
3. Backache or sciatica-like pain, or swelling of the legs that doesn't go away


Normal prostate
Bladder
Seminal vesicle
Prostate
Lymph node

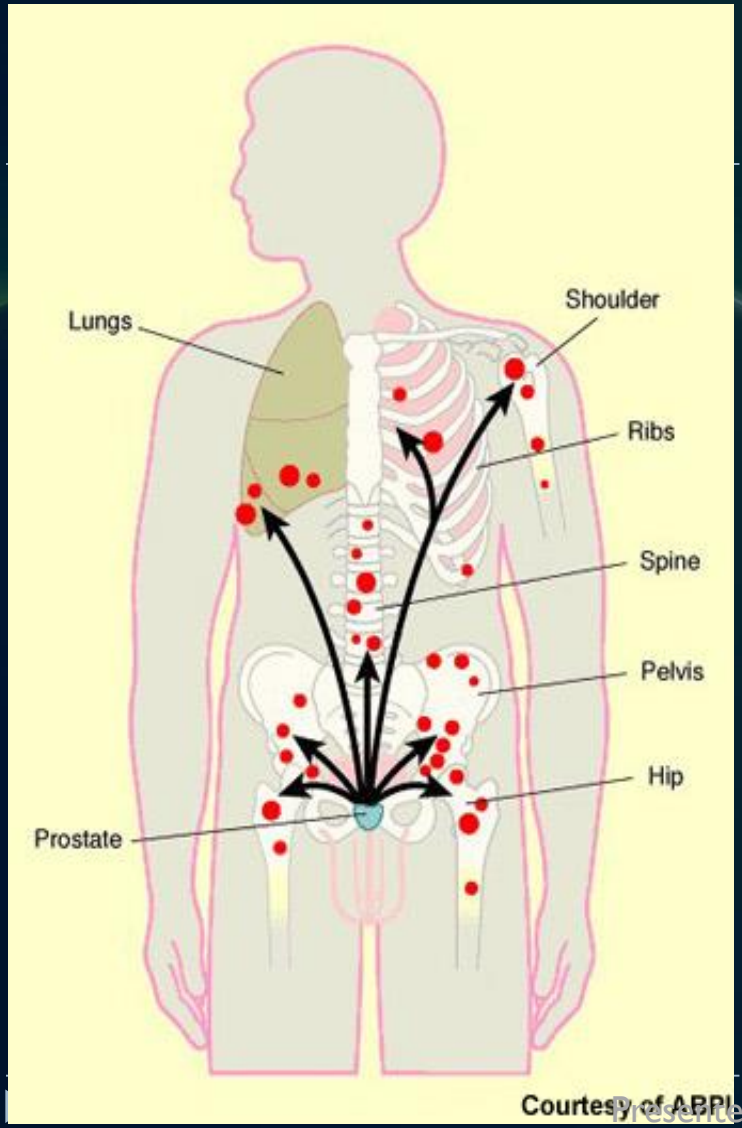
Cancer


Stage I
Stage II
Stage III
Stage IV

PSA level(12)

- Many cases today are detected by PSA levels in the 2.5±10 ng/ml range and are confirmed by histology of biopsies

- Typically, tumours were advanced and extended beyond the organ capsule or had metastasized. In such cases, PSA levels are much higher than 10 ng/ml.



Bone metastases in advanced prostate cancer diagram of sites often affected.

Diagnosis(13)

- Nowadays, an increasing number of prostate cancers are detected through elevated serum PSA levels.
- Before PSA assays became routine, many cases were recognized by digital rectal examination (DRE).

Diagnosis

- Digital rectal examination (DRE)
- PSA blood test – measures the levels of prostate specific antigen.
- Tissue biopsy  TRUS / TURP
- Bone Scan,MRI,CT

Treatment(14)

- To aid in treatment decisions, nomograms have been introduced, which combine information from
  - digital rectal examination,
  - biopsy histology
  - PSA assays

Future aspects

- We are intrested in finding the relevance between this cancer and reduced level of MST1 gene expression to might be achieving this gene as biomarker for early detection of prostate cancer in future researches

REFRENCES

1. O'Neill EE, Matallanas D, Kolch W. Mammalian Sterile 20–Like Kinases in Tumor Suppression: An Emerging Pathway. Cancer research. 2005;65(13):5485-7.
2. Thompson BJ, Sahai E. MST kinases in development and disease. The Journal of cell biology. 2015;210(6):871-82.
3. Glantschnig H, Rodan GA, Reszka AA. Mapping of MST1 Kinase Sites of Phosphorylation ACTIVATION AND AUTOPHOSPHORYLATION. Journal of Biological Chemistry. 2002;277(45):42987-96
6. Huang J, Wu S, Barrera J, Matthews K, Pan D. The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the Drosophila Homolog of YAP. Cell. 2005;122(3):421-34.
7. Pan D. The hippo signaling pathway in development and cancer. Developmental cell. 2010;19(4):491-505.
8. Pan D. Hippo signaling in organ size control. Genes & development. 2007;21(8):886-97.

REFRNCES

- 9. Zhou D, Conrad C, Xia F, Park J-S, Payer B, Yin Y, et al. Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. Cancer cell. 2009;16(5):425-38.
- 10. Waterman M, Xu W, Stempak JM, Milgrom R, Bernstein CN, Griffiths AM, et al. Distinct and overlapping genetic loci in Crohn's disease and ulcerative colitis: correlations with pathogenesis. Inflammatory bowel diseases. 2011;17(9):1936-42.
- 11. Plata BA, Concepcion MT. Prostate cancer epidemiology. Archivos espanoles de urologia. 2014;67(5):373-82.
- 12. Partin A, Yoo J, Carter HB, Pearson J, Chan D, Epstein J, et al. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. The Journal of urology. 1993;150(1):110-4.
- 13. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986–2005. Journal of the National Cancer Institute. 2009;101(19):1325-9.
- 14. Lardy HA, Marwah P, Marwah A. Prostate cancer treatment. Google Patents; 2008.


Thanks for your attention